REMARKS

Claim 1 has been amended to correct the informality noted by the Examiner.

As noted below, the Applicant strongly believes that the application when read as a whole supports and discloses treatment of patients other than those who are being treated for Alzheimer's disease and therefore there is no new matter in the claims presented previously. New claim 41 has, however, been added without this limitation to permit proper consideration of other issues..

The Examiner rejects the application as adding new matter and failing to meet the written description requirement because of the claim limitation restricting the claimed method to persons other than those being treated for Alzheimer's disease. The examiner points out that the only reference to Alzheimer's disease is in the background section of the appllication. However, that is precisely where one would expect to find it when describing the present invention. Paragraph 8 of the specification states that galanthamine has been used for the treatment of Alzheimer's disease. Paragraph 7 refers to WO01/43697 which teaches that other compounds specified in the present invention can be used to treat Alzheimer's disease. There is no rational way in which one can read the present application in its entirety as being a description of a further treatment of Alzheimer's disease. The specification clearly states that use of the specified compounds for such a purpose is known. In no way can the applicant have contemplated use in the treatment of Alzheimer's disease as being her present invention. She had invented the use of galanthamine for this purpose long before. It is true that Alzheimer's disease involves cognitive dysfunction. But it is not the only cause of cognitive dysfunction. The present invention relates to treatment of cognitive dysfunction resulting from a different cause and this is clearly stated in the present specification. It is therefore submitted that when read as a whole, the present specification does teach that the invention described is treatment of cognitive dysfunction other than that caused by Alzheimer's disease and that no new matter is introduced into the specification by stating this explicitly. Nor is there any lack of disclosure of such an invention in the application. The applicant clearly had possession

of the concept of treating a specific cause of cognitive dysfunction separate from that resulting from Alzheimer's disease at the time of filing the application. That cause was, as stated in the present application, cognitive dysfunction caused by low LDL-cholesterol values. As reaffirmed by the Federal Circuit en banc in Ariad v. Eli Lilly 94 USPQ2d 1161 (Fed. Cir. 2010), the purpose of the written description requirement is to show possiession of the invention at the time of filing and that the applicant had really made that invention at that date. Cutting out part of a claim to avoid the possibility that it might cover something that was inherent in the prior art (i.e. treatment of those who had Alzheimer's and so would be treated with the compounds of the present invention for that reason) in no way leads to a conclusion that the applicant lacked possession of the rest of the invention where there can be no question of overlap with anything that is inherent and subjects are being treated with such compounds for a totally different reason, namely their low LDL-cholesterol values.

It is therefore submitted that the requirements of 35 USC 112 first paragraph showing possession of the invention as claimed and 35 USC 132 in not adding any new matter by excluding from the claims treatments that might overlap have problems as covering something that was done unintentionally in prior art treatments of some patients.

Turning now to the obviousness refection, Page 2, paragraph 2, third sentence from the end of the official action reads "Regardless of how cognitive dysfunction occurs, treatment of cognitive dysfunction can be accomplished with nicotinic receptor modulation." The next sentence, which reads "Further, there is nothing to indicate that the patient population indicated in the specification that cognitive dysfunction results from Alzheimer's disease," is hard to understand. A word appears to be missing.

On page 3, paragraph 2, it is stated that "one will not need to take drugs whose primary current use is to treat Alzheimer's disease. This is not persuasive because if there are cognitive defects, regardless of the etiology, galanthamine is a known drug on the marked for treating Alzheimer's disease which is associated with cognitive dysfunctions"

The Applicant asserts that these blanket, unsupported statements are incorrect. Cognitive impairment can result from a variety of conditions for which the treatment

would not be galanthamine. There can be anatomical causes such as tumors, physiological causes such as low perfusion due to cardiac disease, vitamin deficiencies such as B12, hormonal abnormalities such as hypothyroidism or Addison's disease, hyper- and hypocalcemia, medication side effects other than statins, depression, Pick's and Jacob-Creutzfeldt diseases, etc. The treatments for these conditions, where treatable, involve addressing the underlying causes, not the use of galanthamine. Beginning on page 4, the Examiner combines three facts. First, Kivipelto "teaches that high serum cholesterol increases the risk of Alzheimer's disease". Second Simons "teach that there is a decreased prevalence of Alzheimer's disease associated with the use of statins". Third, Davis teaches "that galanthamine is effective in treating Alzheimer's disease."

Kivipelto, as we have discussed in our response of February 13, 2008, and as Simons reviews, associates "elevated midlife cholesterol levels and late-life cognitive impairment." Therefore, statins would be prescribed in midlife. New onset cognitive impairment in a middle aged person is extraordinarily unlikely to be diagnosed as Alzheimer's disease unless the patient is in a rare family with a known genetic mutation. A full history and physical will reveal the new medication, and, if a treatment is desired while the statin continues, a nicotinic receptor modulator could be used to treat the statin side effect. There is no Alzheimer's diagnosis or treatment in such patients.

Simons goes on to review associative, retrospective studies linking statin use with decreased prevalences of Alzheimer's disease. The rest of the article is a selective review of basic science adducing a potential mechanism for a causal relationship. Associational, retrospective studies indicating less Alzheimer's disease in takers of estrogen and anti-inflammatory drugs, supported by preclinical rationales, were not substantiated by prospective, placebo controlled trials. (Aisen et al, 2000; Neurology 54:588-593; Henderson et al, 2000; Neurology 54:295-301; Mulnard et al, 2000; JAMA 283:1007-1015). These failures were known as of 2000, and may underlie Simons et al's call for "double-blind prospective placebo-controlled trials with statins," in patients with AD. (last paragraph, page 1092) in the" hopes that cholesterol-lowering strategies may influence the progression of AD" (abstract). Copies of these are enclosed. As with estrogen and anti-inflammatory drugs, double-blind prospective placebo-controlled trials have since indicated no effect of statins on the incidence of AD (Trompet et al

2010; J Neurol 257(1):85-90; Heart Protection Study Collaborative Group 2004; Lancet 363:757-67). Thus, statins join scores of agents for which there had been mechanistic rationales, and "hope", but which turned out, to no one's surprise in the field, not to be treatments for AD.

(The Simons source articles, Wolozin and Jick, were contemporaneously questioned, even in an accompanying editorial, as discussed in our response of February 13, 2008)

Second section

On page 5, last paragraph before conclusion, the Examiner says the applicants have not provided evidence showing the criticality of 109 mg/dl as an LDL value. The evidence is on page 542, upper right, of Muldoon et al, 2000, which states

> **"Among subjects receiving lovastatin, change in performance was unrelated to the percent change in serum LDL-cholesterol but was significantly related to the post-treatment level (r= .21; P = 0.04). When subjects were divided into those whose final serum LDL-cholesterol level was above or below the medial level, only those in the lower group (who had a mean LDL-cholesterol level at follow-up of 109 ± 11 mg/dL) had a decrease in cognitive function (z score = 0.15; 95% CI, 0.04 to 0.26; P = 0.007).**

Since the average of the cognitively impaired group was 109 mg/dL, and patients with LDL values even higher than the average were impaired, this is certainly a conservative cutoff for patients with impairment.

In any case, nothing in the cited references gives any reason why one skilled in the art would have thought to give galanthamine or any of the other compounds specified in the claims to persons having low LDL-cholesterol values who were not suffering from Alzheimer's disease.

As noted above, the reason for amending the claims to exclude treatment of those being treated for Alzheimer's disease was to avoid the possibility that the claims might unintentionally cover something that was inherent in the prior art namely treatment of a patient who both suffered from Alzheimer's disease and has low LDL cholesterol. Claim 41 does not have the limitation to exclude this possibility. It is, however

submitted that such a claim is permisible because the law on inherency is that to reject a claim on this ground requires inevitability that what is being claimed would have happened, a mere probability is not enough. There has been no such showing in the present case. In re Oelrich 666 F2d 578, 12 USPQ 323 (CCPA 1981).

It is therefore submitted that the present invention meets the requirements of 35 USC 103 and should be allowed.

Respectfully submitted,

JOHN RICHARDS
C/O LADAS & PARRY LLP
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG. NO. 31,053 TEL. NO. (212) 708-1915